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10/764,628	01/26/2004	Veronique Trochon	1002-04	9953

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
01/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pto.phil@dlapiper.com

Office Action Summary	Application No.	Applicant(s)	
	10/764,628	TROCHON ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,17,21 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,17,21 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/26/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/15/09 has been entered. Claims 13, 17, 21 and 25-30 are pending in this application.

Applicants' amendment has been sufficient to overcome the objections to the claims.

Claim Objections

Claims 13, 17, 21 and 25-30 are objected to because of the following informalities: **These are new objections.** The recitation "an expression plasmid coding for the disintegrin domain consisting of the sequence shown in SEQ ID NO:2 where the disintegrin domain consisting of the sequence shown in SEQ ID NO:2 is encoded by a polynucleotide sequence operably linked to a promoter or expression control sequence" can be simplified for more clarity to -- an expression plasmid coding for the disintegrin domain consisting of SEQ ID NO:2 where the disintegrin domain is encoded by a polynucleotide sequence operably linked to a promoter or expression control sequence--. The amendment removes the redundant recitation that the disintegrin domain "consisting of SEQ ID NO:2". As well, a sequence is not "shown in " a SEQ ID NO; but rather is the sequence within the SEQ ID NO:. Therefore, "shown in" is incorrect in each of the claims.

Furthermore, claims 13, 17 and 21 intend as evidenced by applicants' arguments regarding the art rejection to require distinct subjects i.e. any subject with intratumoral vessels, a subject with melanoma and a subject with pulmonary metastases. For completeness, it would be clearer to recite , --A method of treating a mammal with melanoma by decreasing-- in claim 17 and --A method of treating a mammal with pulmonary metastases by decreasing--.

In claims 25, 27 and 29, the claims can also be simplified to recite --said polynucleotide sequence consists of SEQ ID NO:1--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 17, 21 and 25-30 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of direct injection to a melanoma or a pulmonary metastasis of a nucleic acid consisting of SEQ ID NO: 1 operably linked to an expression control sequence, followed by application of electric field pulses to the melanoma or the pulmonary metastasis wherein expression of SEQ ID NO:1 results in the decrease in the number of intratumoral vessels and in inhibition of growth of the melanoma or inhibition of the pulmonary metastases, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

This rejection is maintained for reasons set forth 7/9/08 and 4/15/09 and restated below. New claims 25-30 have been added to the rejection.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a methods of decreasing the number, or formation of intratumoral vessels in a mammal, in a mammal with melanoma and in a mammal with pulmonary metastases by direct inoculation and electrotransfer of a nucleic acid consisting of the polynucleotide sequence of SEQ ID NO:1 operably linked to an expression control sequence. The specification teaches that the disintegrin domain of metargidin when delivered to a tumor or metastases site can cause a diminution of vessels and thus lead to a decrease in pulmonary metastases and melanoma growth. The method recites quite broadly that the nucleic acid is delivered by electrotransfer to an intramuscular site or an intratumoral site. First, it is not clear what relationship the intratumoral site or intramuscular site have to the intratumoral vessels. Hence, the nucleic acid is introduced intramuscularly or intratumorally but if this site is to be adjacent or consistent with the intratumoral vessels is unclear. This leads to issues of unpredictability described more completely below. Briefly, gene therapy is hindered by methods

of introduction that are not direct. Secondly, while the claims recite that the disintgerin domain "consists" of SEQ ID NO:1, this does not limit the context into which the sequence can be found.

The disintegrin domain constitutes Met 420 to Gly 511 of the full-length metargidin. However, SEQ ID NO:1 does not encode all of the metargidin. Rather, SEQ ID NO:1 encodes **the** disintegrin domain of metargidin and this disintegrin domain is encoded by all of SEQ ID NO:1. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures and functions proapototically independent of modification of their cell cycle. Metargidin is a member of the adamalysin family (ADAMS) which functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are

viable options against diseases. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b)." First, the claimed method steps require direct inoculation and electrotransfer to an intramuscularly or intratumorally site. In this case, the claim does not set forth the relationship of the site of inoculation and the target site. For example, to what the inoculation is direct. As well, it is not clear what steps of the method of "direct inoculation and electrotransfer" are as disclosed by the specification. There is a single example of electrotransfer in ¶ 0095 wherein the plasmid is injected into the tibia cranial muscle of mice and following that 8 electric shocks of 200 V/cm were applied to the mouse. Hence, the specification teaches, injection intramuscularly followed by application of electric shock to electrotransfer the plasmid DNA into the muscle cells. This method is supported by Mir which teaches that the DNA must be injected into the tissue followed by delivery of electrical pulses to the target tissue, the order cannot be reversed (see page 169, col 2) that is strictly local (see e.g. page 170, last ¶). Local

transfer is required as concentration of DNA is low and thus is sensitive to dilution (see page 171, ¶ 2) and thus injection and electric pulses must be limited to the target site.

Further regarding methods of transfer, the art teaches that the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. In fact, the specification teaches, "Likewise, most transgenic protein expression is mostly, though not exclusively, restricted to the injection site. Such experiments have failed to demonstrate widespread expression of transgenic proteins in the brain beyond two months". As well, Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery.., the problem has been an inability to deliver genes efficiently and to obtain sustained expression". The unpredictability associated with viral based therapies has been recently highlighted in the art, see for example, Check, Nature, 2003. Leakiness of and dissemination to tissues surrounding the targeted area and hence expression of receptor in non-targeted cells is particularly lethal, "dissemination of the vector particle itself can have harmful consequences; lack of adenovirus vector specificity was directly linked to the induction of the massive systemic immune response that caused the death of Jesse Gelsinger in 1999 (see Thomas page 354, col 1). Even use of tissue specific or inducible promoters cannot offset these ill effects. Vector tropism, the duration of transgene expression and vector immunogenicity are other factors that influence the suitability of a vector for specific therapeutic applications (see Thomas, page 348, col 2). "Lentiviral transduction of muscle and liver has also been shown in animals, but, interestingly, studies in the liver have indicated that not all non-dividing cells are equally susceptible to transduction by lentivirus vectors; some cell

types (such as the hepatocyte) might require cell cycling for efficient gene transfer in vivo (see Thomas, page 348, col 2)." To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. In more advanced studies related to cancer, the art teaches "to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (Russell page 1165, col 2,¶ 4-5).

Furthermore, in vitro and animal models have not correlated well with in vivo clinical trial results in patients. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograph and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno- deficient mice" (Meng and Diery p. 6, column 1). The success of any in vitro assays or in vivo animal models cannot be considered as evidence of success of treatment, in vivo results rarely correlate well with in vivo clinical trial results in patients and have not translated into successful human therapies. Many in vitro and animal models that are provided as evidence of success of treatment have not translated into successful treatments in humans. Ultimately the mouse model predicts agents that are effective in treating mice but not humans (see Gura, e.g. page 1041, col 1 and col 2, last paragraph). Therefore, the ability to predict potential success in humans based upon experimental results is highly unpredictable as demonstrated by the art. Rather for humans direct administration appears necessary to reduce non-desirable effects as well as to ensure full effect of delivered biomolecules

The invention recites use of a direct inoculation and electrotransfer of nucleic acid encoding the disintegrin domain to any muscle or tumor to decrease the number of formation of intratumoral vessels in a mammal. Given the unpredictability of the art with regard to nucleic acid stability once administered, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Response to Amendments

Applicants' response filed on 10/09/09 has been considered but are not persuasive for the following reasons. Applicants have amended the claims to indicate that the nucleic acid is administered by direct inoculation and electrotransfer intramuscularly or intratumorally. The instant method requires treatment of pulmonary metastasis and/or melanoma. First, and as set forth above, it is not clear what relationship exists between the target site and the muscle or tumor receiving the nucleic acid. This is exacerbated by the unpredictable nature of gene therapy to avoid ancillary effects that are not desired as well as loss of function due to dissemination of the nucleic acid from the target site.

Applicants argue that the scope of the claims as recited is consistent with the rejection. However, the rejection states that the nucleic acid is not directly administrated to the melanoma or pulmonary metastasis. In fact, there is no requirement of a site of inoculation and it is not clear to what the nucleic acid is directly inoculated. It is noted that the rejection did not reference "inoculation" but rather administration or more specifically injection. Applicants argue that the specification and the Declaration filed 5/8/07 teach that injection into the tibial muscle followed by electrotransfer inhibits growth and vascularization of tumors in the back and

inhibited the number of pulmonary metastases. The Declaration demonstrated intratumoral injection followed by electrotransfer also inhibited growth of melanoma cells. In this regard, the art teaches that for therapeutic results, methods of administration are unpredictable. It is accepted that direct injection of DNA will reduce the dilution of the sequence such that therapeutic levels of peptide can be achieved without harmful affects of vector encountered when the delivery is not local. Add to that the teachings of Mir et al which support use of local administration and electric pulses for predictable results. Applicants provide animal data to support the contention that the method does not require local administration. However, as set forth above, results in animals cannot be extrapolated with confidence to reflect predictable results in humans, who are the intended target for this method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 17, 21 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettan et al (Bioelectrochemistry, 2000, pages 83-90; see entire document) in view of Fanslow et al (US 7,074,408; see entire document) and as evidenced by or further in view of Merkulov et al (US 6,294,368; see entire document). **This rejection is maintained for reasons set forth 4/15/09 and restated below. New claims 25-30 have been added to the rejection.**

Applicants claim a method of decreasing intratumoral vessels to inhibit growth of melanoma and pulmonary metastases in a mammal by administering SEQ IDNO:1.

Bettan et al teach methods of treating tumors and angiogenesis (production of tumoral vessels) by electrotransfer intratumorally. Bettan et al speak to the success of intramuscular administration in animals. Bettan et al do not speak to the nature of the gene to be introduced.

Fanslow et al teaches that disintegrin domains from a variety of ADAM proteins such as metargidin can be used to inhibit angiogenesis and endothelial cell migration (see e.g. abstract and table 1). Fanslow et al do not provide the sequences used but as evidenced by Merkulov et al, the sequence is the same as SEQ ID NO:1.

As well, Merkulov et al isolate a protein comprising SEQ ID NO:11 (alignment below) and teaches that it is highly related to the ADAM disintegrins (see e.g. col 7, line 10-26). Merkulov propose administration of this molecule for treatment modalities (see e.g. bridging ¶ col 15-16).

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Query Match             100.0%;  Score 549;  DB 4;  Length 814;
  Best Local Similarity   100.0%;  Pred. No. 4.1e-34;
  Matches   91;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 MAAFCGNMFVEPGEQCDCGFLDDCVDPCCDSLTCQLRPGAQCASDGPCCQNCQLRPSGWQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        420 MAAFCGNMFVEPGEQCDCGFLDDCVDPCCDSLTCQLRPGAQCASDGPCCQNCQLRPSGWQ
479

Qy         61 CRPTRGDCDLPEFCPGDSSQCPPDVSLGDGE 91
              |||||||||||||||||||||||||||||||
Db        480 CRPTRGDCDLPEFCPGDSSQCPPDVSLGDGE 510
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It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the disintegrin domain comprising protein taught by Merkulov et al or the

disintegrin domain as taught by Fanslow et al in the methods taught by Bettan et al because Merkulov et al and Fanslow et al teach that it is within the ordinary skill of the art to use proteins comprising disintegrin domains of metargidin in treatment of cancer and vessel formation and because Bettan et al teach that it is within the ordinary skill of the art to target treatments by electrotransfer into the tumor. As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith* --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, it is obvious to combine known technologies with known products for predictable results and Bettan et al teach that it is known to administer treatment modalities on expression vectors encoding the product by electrotransfer and Merkulov and Fanslow et al teach that disintegrin domains provide successful therapeutic modalities. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Amendments

Applicants response filed on 1/8/09 have been considered but are not persuasive for the following reasons. To this end, applicants argue that the art rejection cannot stand given the rejection under 35 USC 112, first paragraph and that both the enablement rejection and the art rejection should be withdrawn. However, the instant claims are rejected under 35 USC 112, first paragraph as comprising enabled subject matter. In other words, the claims do not completely lack enablement. The basis of the enablement rejection is 1) the claims as written lack clarity

which extrapolates an unpredictable art and hence the stated goal requires additional steps and 2) coupled with the unpredictability of methods of administration for the recited outcome, the skilled artisan would clearly have to engage in undue empirical experimentation to confirm that the claimed method could be as recited. Such an enablement rejection does not argue that the anticipated method steps are not enabled but that the method steps require limiting the large breadth of the recited subject matter to that that is enabled. For example, direct injection to a target site of a nucleic acid followed by direct electric pulses as taught by Bettan et al. Specifically, Bettan teaches that electrotransfer following direct transfer provides a predictable means of administering nucleic acids of interest to target sites. Bettan et al teach direct injection of the plasmid into the tumor or site of action and thus does not read on the non-enabled aspects as set forth above (see e.g. section 2.3, page 84). Hence, Bettan reads on the enabled scope of the claims. As well, applicants argue that the claims recite intratumoral and intramuscular and because Bettan only teaches intramuscular, it does not encompass all of the limitations of the claim. However, the claim recites that the site of administration can be "intramuscular or intratumoral" and hence it need not be both.

Fanslow et al teach methods of inhibiting angiogenesis or vascular formation by introduction of compositions comprising ADAM disintegrin domains. Applicants argue that Fanslow et al 1) do not teach use of only the 91 amino acid domain of the instant claims 2) does not demonstrate that the disintegrin domain alone is capable of activity and in fact teaches against expressing the disintegrin domain alone because the polypeptide is not stable and other molecules show superior results 4) do not teach treatment of melanoma or pulmonary metastases. However, the broad breadth of the claims means that they do not require any of the above, i.e.

that the molecule administered is only the 91 amino acid disintegrin domain or that the mammal explicitly have melanoma or pulmonary metastases. "While it is appropriate to use the specification to determine what applicant intends a term to mean, a positive limitation from the specification cannot be read into a claim that does not itself impose that limitation. A broad interpretation of a claim by USPTO personnel will reduce the possibility that the claim, when issued, will be interpreted more broadly than is justified or intended. An applicant can always amend a claim during prosecution to better reflect the intended scope of the claim." MPEP 2105. The claim language is so broad as to encompass molecules comprising a disintegrin domain wherein the nucleic acid is introduced into any mammal. The nucleic acid encoding disintegrin must consist of the sequences of SEQ ID NO:2. The vector however, is not limited to only those sequences. Rather, the vector can comprise any number of other sequences so long as it has a disintegrin domain that is limited by consisting of SEQ ID NO:2. A more narrow limitation can be attained by reciting --an expression cassette encoding a therapeutic peptide that consists of SEQ ID NO:2 absent any operably linked coding sequences--. However, there is no requirement in the claim that the domain be alone only that it be in the instant vector. To this end, however, it is noted that Fanslow et al actually do recognize that the domain alone can be used.

> "The present invention encompasses the use of various forms of ADAM disintegrin domains that retain at least one activity selected from the group consisting of integrin binding activity, inhibition of endothelial cell migration, and inhibition of angiogenesis. The term "ADAM disintegrin domain polypeptide" is intended to encompass polypeptides containing all or part of a native ADAM disintegrin domain, with or without other ADAM domains (such as the cysteine-rich region), as well as related forms including, but not limited to: (a) fragments, (b) variants, (c) derivatives. (d) fusion polypeptides, and (e) multimeric forms (multimers). The ability of these related forms to inhibit integrin binding endothelial cell migration, and/or inhibition of angiogenesis may be determined in vitro or in vivo by using methods such as those exemplified below or by using other assays known in the art. (col 5, line 39-54)"

The claims by recitation that melanoma is treated in a mammal in need thereof, does not limit the mammal to one that has melanoma but one that needs treatment against melanoma. And while other molecules in Fanslow et al show superior results, the invention cannot be limited to the exemplified methods but to that which is disclosed and Fanslow discloses that each of the molecules can be used therapeutically. Fanslow et al teach use of ADAM 15 which shares the sequence of SEQ ID NO:2 as demonstrated by Merkulov et al.

Finally, applicants argue that the instant results were unexpected as it was not known if the disintegrin domain alone was stable. To the contrary, there are numerous teachings in the art that the disintegrin domain can function alone and is preferable alone (see Fanslow et al cited above). In fact, Fanslow et al teaches that these domains *can* be used as fusions but does not limit the operability to fusions. "In some embodiments a therapeutically effective amount of the ADAM disintegrin domain is administered to a mammal in need of such treatment (bridging ¶ col 3-4)."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633